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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/800,448	03/05/2001	Santu Bandyopadhyay	A34065	2808

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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/800,448	BANDYOPADHYAY ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-21,23-26,28-36 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-21,23-26,28-36 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 9/25/06, are acknowledged.

2. Claims 14-21, 23-26, 28-36, and 38 are pending.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 14-21, 23-26, 28-36, stand 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method would result in mature DLCs as claimed.

As set forth previously, A review of the specification discloses that the method of the instant claims comprises culturing monocytes or bone marrow cells with platelets, said culture resulting in mature DLCs. A review of the art shows that bone marrow includes multiple cell types including stromal cells, red blood cells, and white blood cells, including monocytes, but also including eosinophils and other unrelated white blood cells, see for example, *Wikpedia*. It is unclear how unrelated and terminally differentiated cell types such as red cells or stromal cells can be cultured into mature DLCs. Given that the specification discloses only the use of human monocytes and undefined mouse bone marrow cells, and further given that there is no evidence of record that cells can be dedifferentiated and transformed into an unrelated cell type, it is most likely that only the monocytes found in the mouse bone marrow actually cultured into mature DLCs. Accordingly, the method of the instant claims are not enabled as broadly claimed.

Additionally, there is no evidence of record that the method of the instant claims actually results in a mature DLC. As set forth in Brand et al., LC-specific markers, e.g., the Lag antigen were known in the art at the time of the invention. Curiously, the product cells of the instant claims were not assayed for such markers to confirm their identity. Several markers were, however, assayed. As further set forth in Brand et al., CD1a should be found on essentially all DLCs, yet the specification discloses that "only approximately 20%" of the product cells of the instant claims displayed this marker. The reference further teaches that a mature DLC would also be expected to express CD80, yet again, the specification discloses that "only approximately 20%" of the

product cells of the instant claims displayed this marker. Likewise, a mature DC of any type would be expected to express high levels of CD83, yet again, the specification discloses that "only approximately 20%" of the product cells of the instant claims displayed this marker. Accordingly, in view of the disclosed results, it is unclear how the cells obtained by the method of the instant claims can be considered to be DLCs.

Of further note is the cell type to which the asserted DLCs of the claimed method are compared, i.e., monocytes matured in GM-CSF and IL-4. As set forth in Romani et al., the culture development of LCs from precursor cells in culture requires either TNFα, or more preferably, TGFβ1. Absent either of these cytokines it is unclear what the cells of the claimed method were actually compared to. It is clear, however, that they were not compared to LCs.

Given the demonstrated unpredictability of the art, i.e., that differences in the cytokine milieu in which precursor DCs are cultured results in different cell products, claims reciting a method of culturing cells resulting a single, specific cell type such as this, absent any sort of showing, or even sound scientific reasoning, in support, must be considered unpredictable and requiring of undue experimentation.

Applicant's arguments, filed 9/25/06, have been fully considered but they are not persuasive. Applicant argues that "the Examiner is improperly requiring that the claimed method function perfectly, that is, that every cell present in the preparation should give rise to a DLC".

A more accurate description of the Examiner's position would be that the claimed method encompasses embodiments that would not function at all. Applicant's arguments would be more appropriate for a method employing whole or unfractionated bone marrow. The instant claims recite no such limitation. As currently recited, the claimed method encompasses the use of any cell type that can be found in bone marrow.

Applicant argues that the operation of the claimed invention need not be shown "beyond a reasonable doubt".

A set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. In the instant case, the skilled artisan would not likely accept that *any* cell selected from bone marrow could be turned into a DLC.

Applicant asserts that "the distinction between mature and immature DLCs does not lie in the absolute presence or absence

of expression of particular cell surface markers, but instead depends upon the ability of the DLCs to stimulate T-cells".

Applicant is advised that cell types are routinely identified and characterized by the cell surface markers they express. By Applicant's function-only definition a B cell could be considered a DLC because under some conditions a B cell can stimulate a T cell. Curiously, Applicant follows the assertion by attempting to identify the DLCs of the claims with different cell surface markers (MHC class II, CD40, CD86). As set forth above, such a small percentage of the DLCs of the claims express other appropriate cell markers (CD1a, CD80, CD83) as to call into the question the actual cell type(s) obtained by the claimed method. Clearly, enough question has been raised such that the skilled artisan would not accept without question that the claimed method would result in mature DLCs.

Applicant argues that the skilled artisan could test the cells obtained by the claimed method to determine whether or not they are DLCs.

Applicant's argument raises two issues, first, Applicant is suggesting a trial-and-error approach, i.e., try the method and see if it produces DLCs. Methods of trial-and-error are not generally considered to be enabled because they do not present an expectation of success. Second, whether or not the skilled artisan could test the cells obtained by the claimed method is irrelevant, the standard is whether or not the skilled artisan would accept without question the functionality of the claimed method. It remains the Examiner's position that the skilled artisan would not.

5. Claims 32 and 33 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection. **NOTE:** previous rejections part A)-C) have been withdrawn in view of Applicant's amendment.

As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

D) a method … wherein more than about 50% display reactivity to anti-HLA-DR, anti-CD40, and anti-CD86 monoclonal antibodies and approximately 20% of the

mature dendritic cells display reactivity to anti-CD1a, anti-CD80, and anti-CD83 monoclonal antibodies (Claim 32).

Regarding D), the cite at page 8 relied on for support, discloses only a single experiment employing only human monocytes incubated in serum free medium with autologous platelets. Additionally, the cite discloses "only approximately 20%" and not the "approximately 20%" of the claim. This is not the broad method of the claim.

Applicant's arguments, filed 9/25/06, have been fully considered but they are not persuasive. Applicant argues that the example at pages 7-9 of the specification show a reduction to practice and thus satisfy the written description requirement.

The Examiner agrees that the example does indeed show a reduction to practice, but only of a method employing human monocytes incubated in serum free RPMI-1640 medium with autologous platelets. Said method is not the generic method of the instant claims.

6. The following are new grounds for rejection necessitated by Applicant's amendment.

7. Claims 14-21, 23-26, 28-36, and 38 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) a method comprising … monitoring the cultured cells for the appearance dendritic processes, and markers associated with dendritic Langerhans cells, (Claims 14, 23, 28-30 and 32).

B) a method … wherein the peripheral blood monocytes are rat cells, (Claim 30).

Regarding A), Applicant indicates support for the new limitation at pages 7-8 of the specification.

Pages 7-9 of the specification discloses a single experiment employing only human monocytes incubated with autologous platelets in serum free RPMI-1640 medium. The cite

does not disclose the broad method of the instant claims which would encompass the use of monocytes or bone marrow cells from any source. Further, the cite does not disclose the generic "monitoring" of the cultured cells for the appearance dendritic processes and markers associated with dendritic Langerhans cells.

Regarding B), Applicant has offered no support for this new limitation and none has been found.

8. No claim is allowed.

9. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

11. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Inquiries of a general nature may also be directed to the Technology Center 1600 Receptionist at (571) 272-1600.

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11/16/06